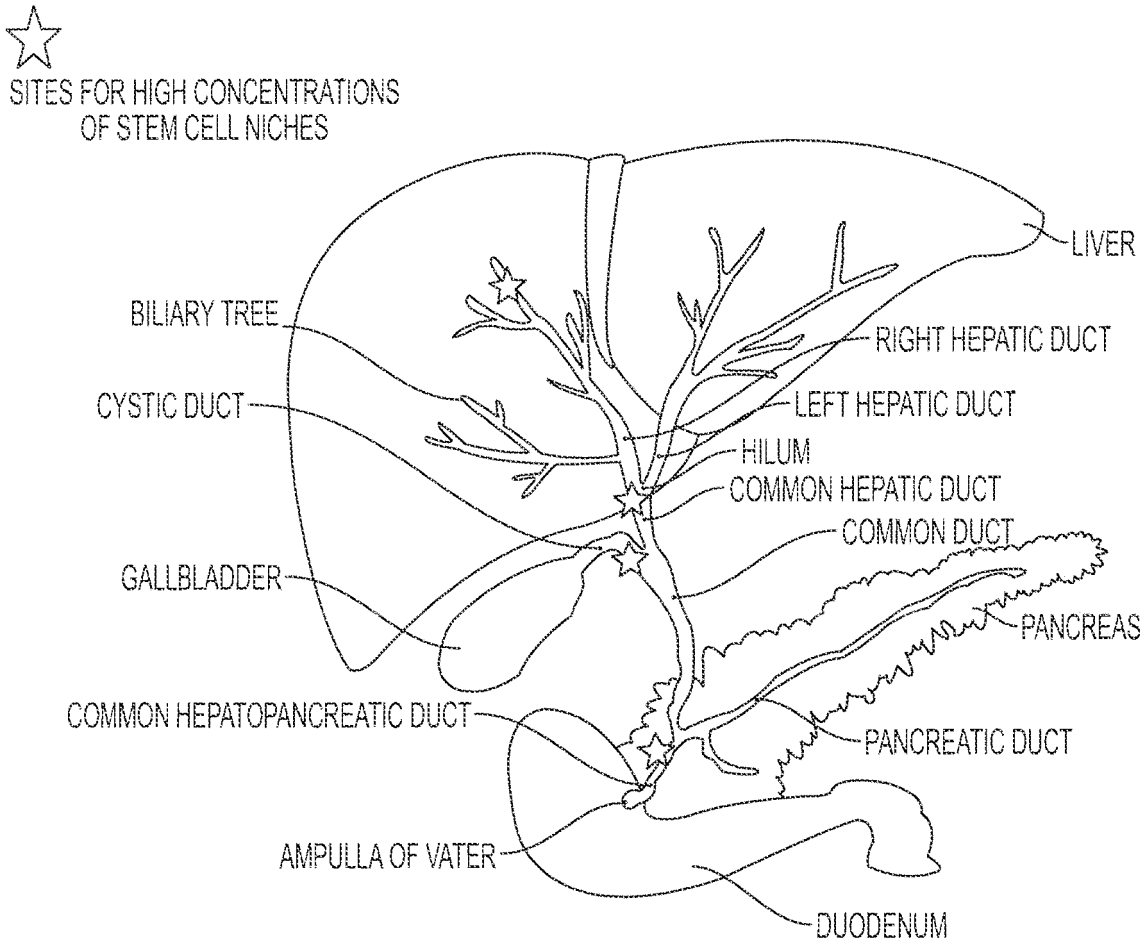

SITES FOR HIGH CONCENTRATIONS OF STEM CELL NICHES
LIVER
BILIARY TREE
RIGHT HEPATIC DUCT
CYSTIC DUCT
LEFT HEPATIC DUCT
HILUM
COMMON HEPATIC DUCT
COMMON DUCT
GALLBLADDER
PANCREAS
COMMON HEPATOPANCREATIC DUCT
PANCREATIC DUCT
AMPULLA OF VATER
DUODENUM

FIG. 1

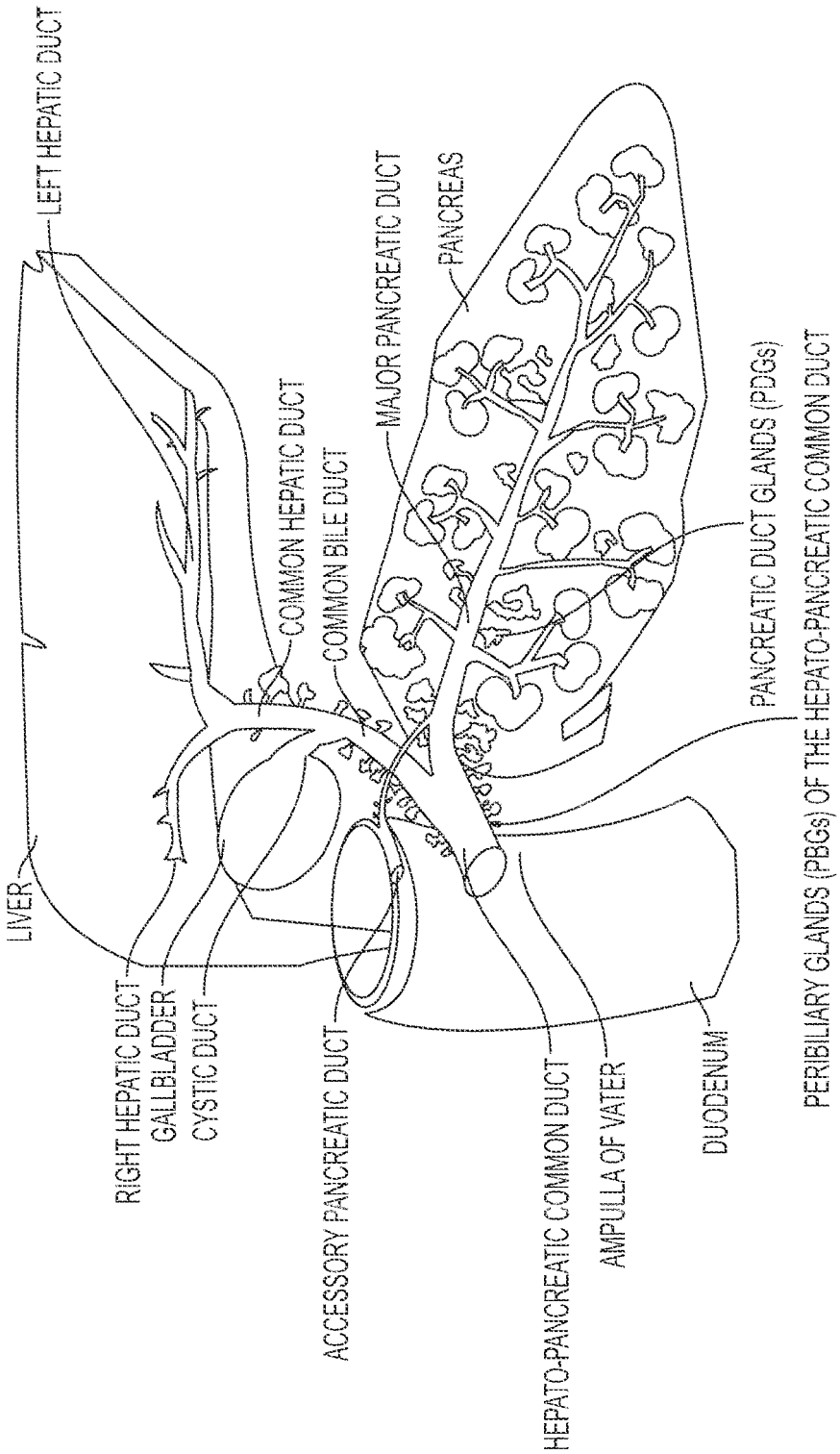

LEFT HEPATIC DUCT
COMMON HEPATIC DUCT
COMMON BILE DUCT
MAJOR PANCREATIC DUCT
PANCREAS
PANCREATIC DUCT GLANDS (PDGs)
PERIBILIARY GLANDS (PBGs) OF THE HEPATO-PANCREATIC COMMON DUCT
LIVER
RIGHT HEPATIC DUCT
GALLBLADDER
CYSTIC DUCT
ACCESSORY PANCREATIC DUCT
HEPATO-PANCREATIC COMMON DUCT
AMPULLA OF VATER
DUODENUM

FIG. 2

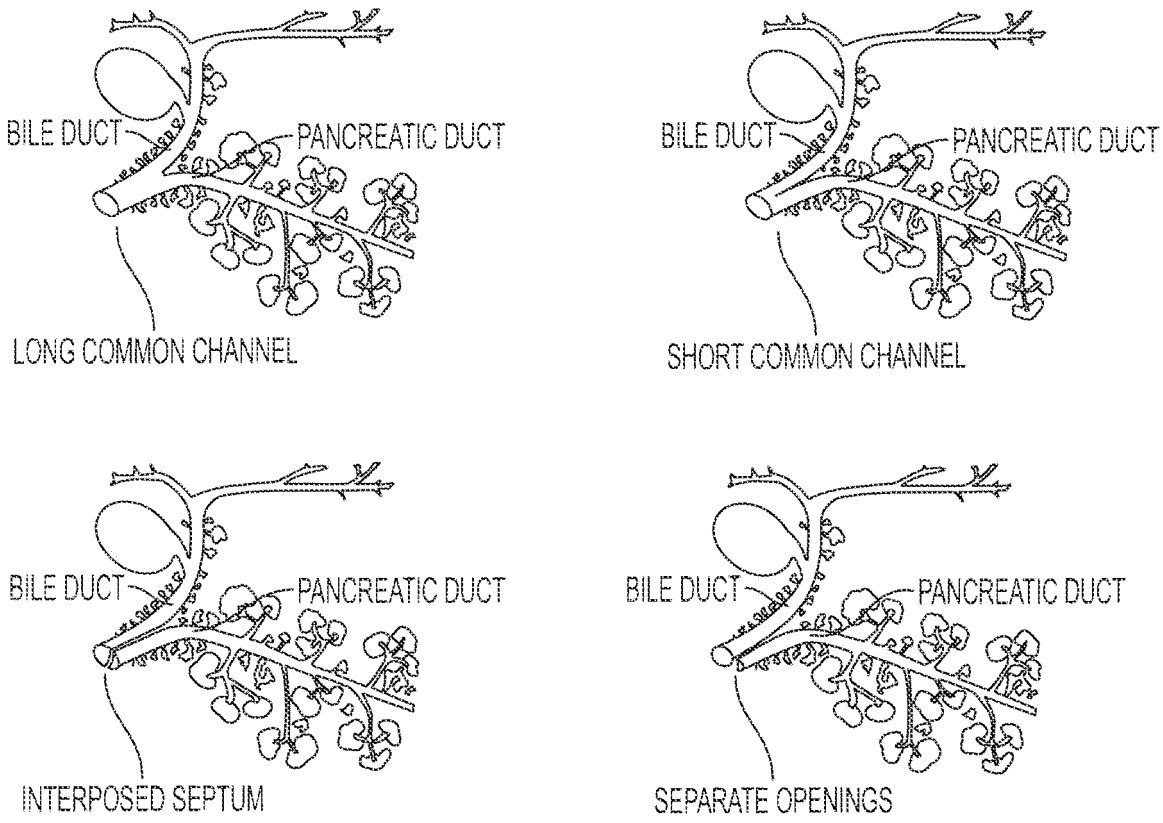

BILE DUCT
PANCREATIC DUCT
LONG COMMON CHANNEL
BILE DUCT
PANCREATIC DUCT
SHORT COMMON CHANNEL
BILE DUCT
PANCREATIC DUCT
INTERPOSED SEPTUM
BILE DUCT
PANCREATIC DUCT
SEPARATE OPENINGS

FIG. 3

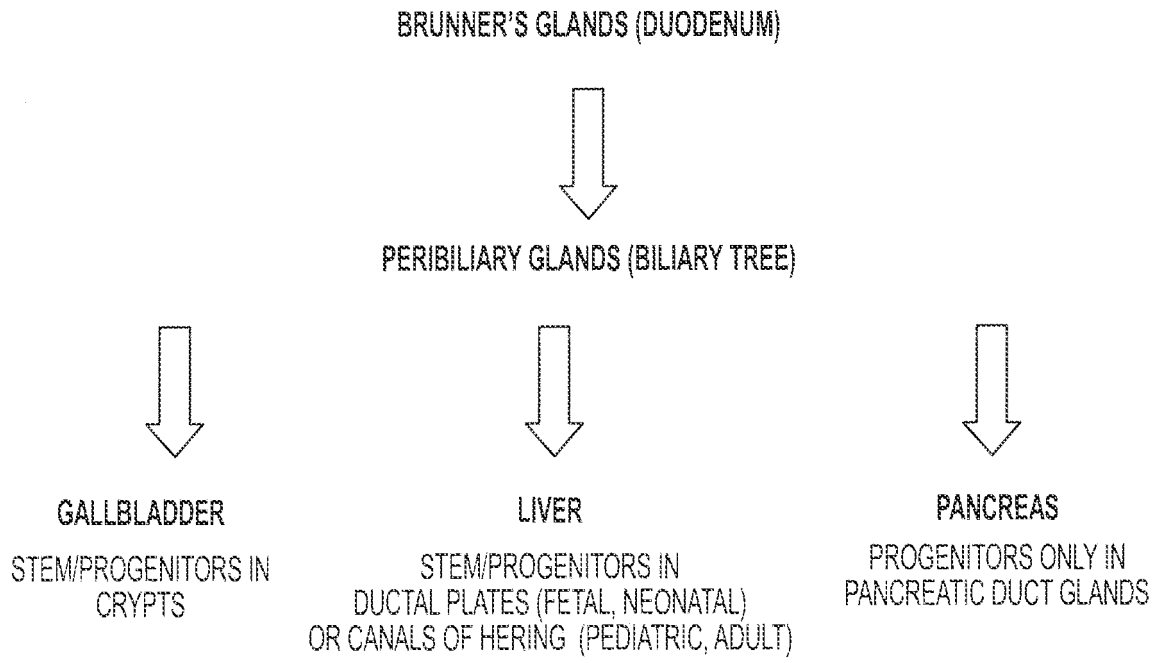
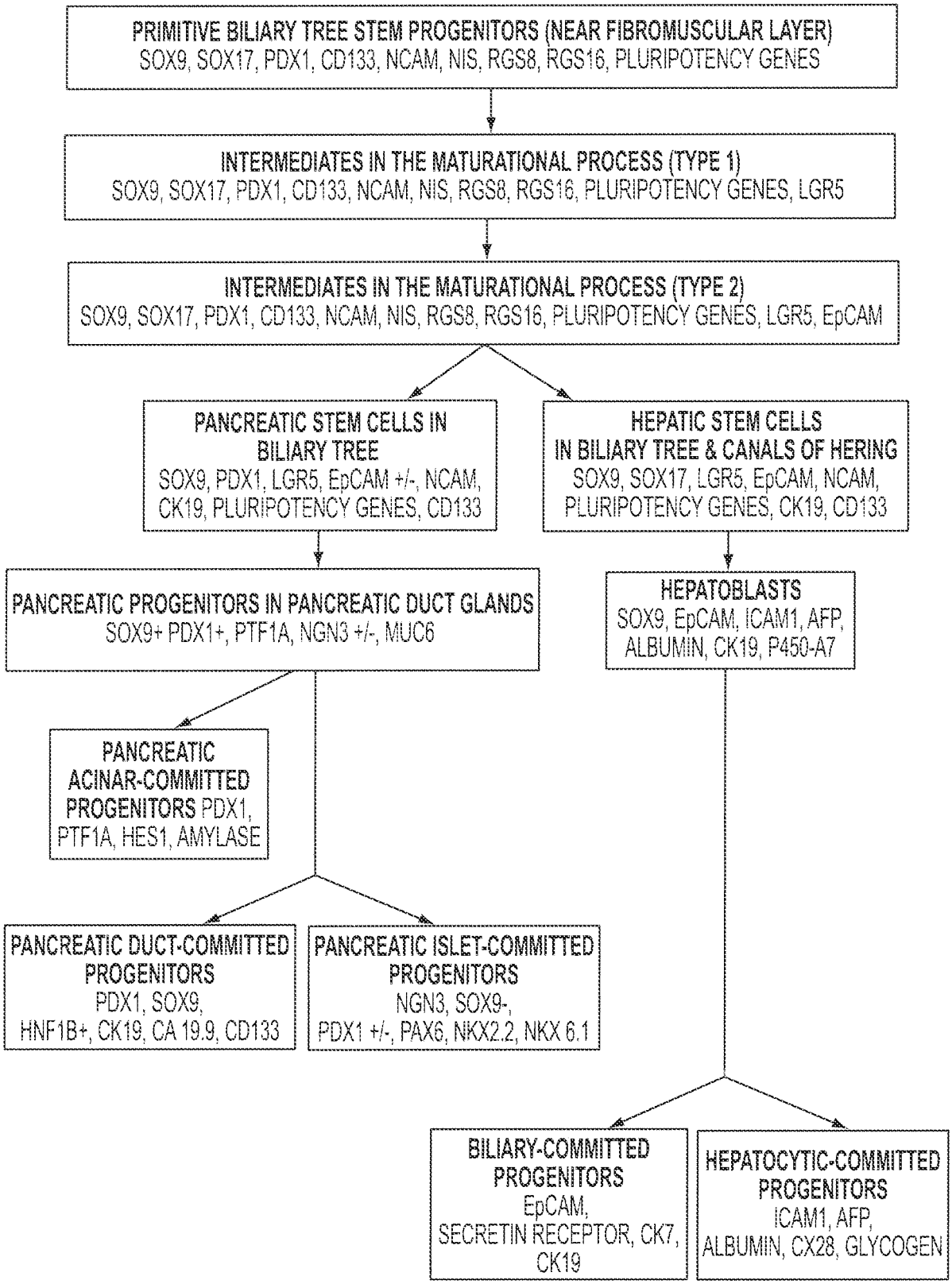

BRUNNER'S GLANDS (DUODENUM)
PERIBILIARY GLANDS (BILIARY TREE)
GALLBLADDER
STEM/PROGENITORS IN CRYPTS
LIVER
STEM/PROGENITORS IN DUCTAL PLATES (FETAL, NEONATAL) OR CANALS OF HERING (PEDIATRIC, ADULT)
PANCREAS
PROGENITORS ONLY IN PANCREATIC DUCT GLANDS

FIG. 4



PLURIPOTENCY GENES: SOX2, OCT4, KLF4, NANOG, TROP-2, BMI-1, SALL4
CELL AT ALL MATURATIONAL LINEAGE STAGES EXPRESS CYTOKERATINS 8 AND 18

FIG. 5

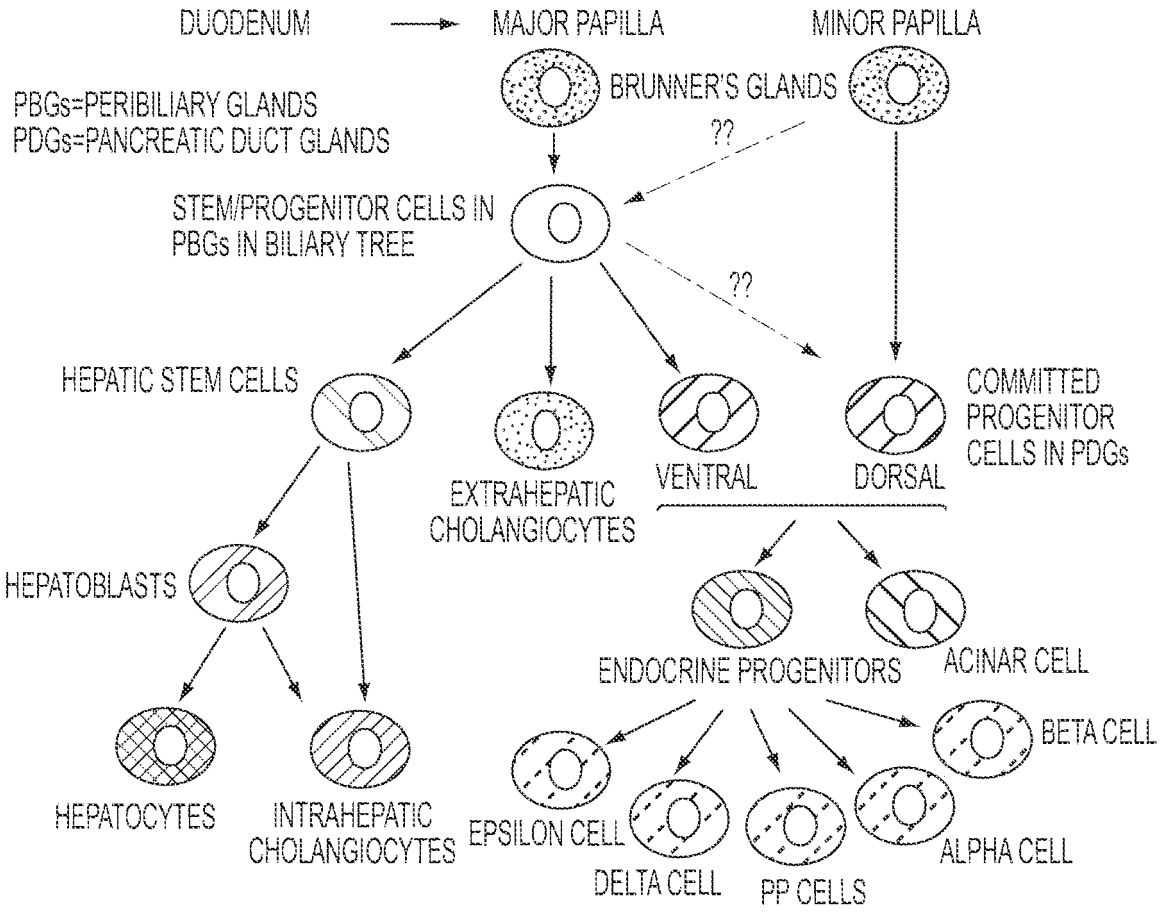

DUODENUM
MAJOR PAPILLA
MINOR PAPILLA
BRUNNER'S GLANDS
PBGs=PERIBILIARY GLANDS
PDGs=PANCREATIC DUCT GLANDS
??
STEM/PROGENITOR CELLS IN
PBGs IN BILIARY TREE
??
HEPATIC STEM CELLS
EXTRAHEPATIC
CHOLANGIOCYTES
VENTRAL
DORSAL
COMMITTED
PROGENITOR
CELLS IN PDGs
HEPATOBLASTS
ENDOCRINE PROGENITORS
ACINAR CELL
BETA CELL
HEPATOCYTES
INTRAHEPATIC
CHOLANGIOCYTES
EPSILON CELL
DELTA CELL
PP CELLS
ALPHA CELL

FIG. 6

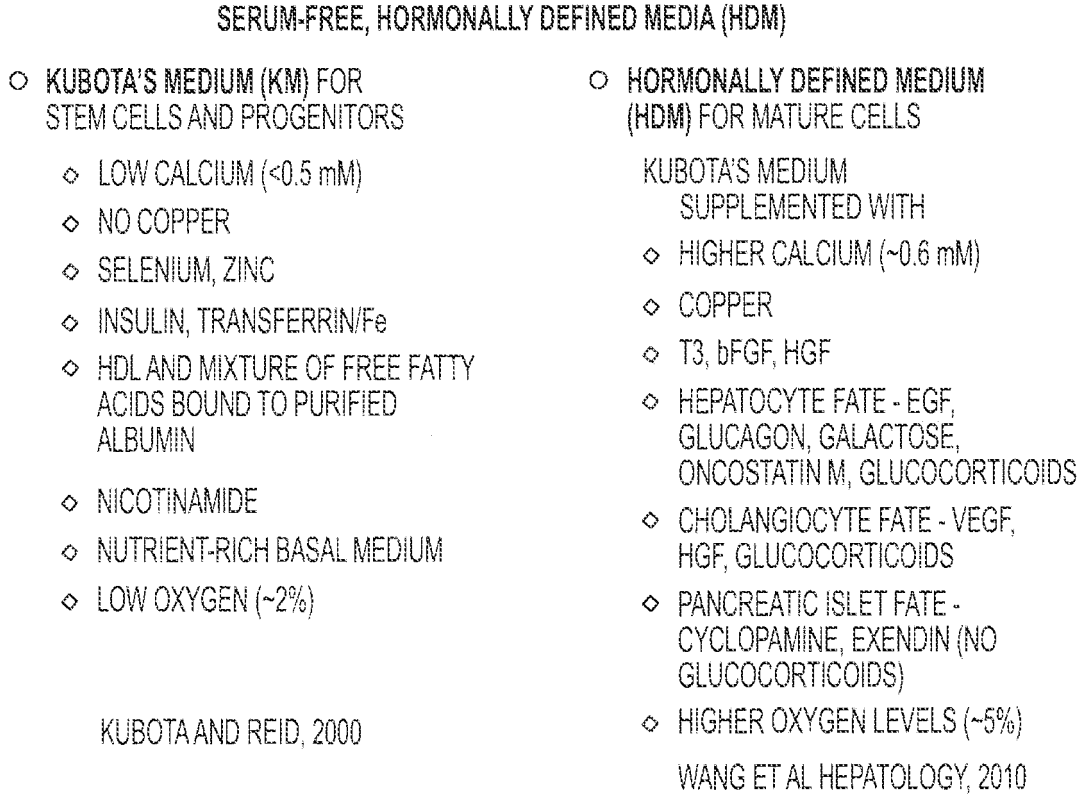

SERUM-FREE, HORMONALLY DEFINED MEDIA (HDM)
KUBOTA'S MEDIUM (KM) FOR STEM CELLS AND PROGENITORS
LOW CALCIUM (<0.5 mM)
NO COPPER
SELENIUM, ZINC
INSULIN, TRANSFERRIN/Fe
HDL AND MIXTURE OF FREE FATTY ACIDS BOUND TO PURIFIED ALBUMIN
NICOTINAMIDE
NUTRIENT-RICH BASAL MEDIUM
LOW OXYGEN (~2%)
KUBOTA AND REID, 2000
HORMONALLY DEFINED MEDIUM (HDM) FOR MATURE CELLS
KUBOTA'S MEDIUM SUPPLEMENTED WITH
HIGHER CALCIUM (~0.6 mM)
COPPER
T3, bFGF, HGF
HEPATOCYTE FATE - EGF, GLUCAGON, GALACTOSE, ONCOSTATIN M, GLUCOCORTICOIDS
CHOLANGIOCYTE FATE - VEGF, HGF, GLUCOCORTICOIDS
PANCREATIC ISLET FATE - CYCLOPAMINE, EXENDIN (NO GLUCOCORTICOIDS)
HIGHER OXYGEN LEVELS (~5%)
WANG ET AL HEPATOLOGY, 2010

FIG. 7

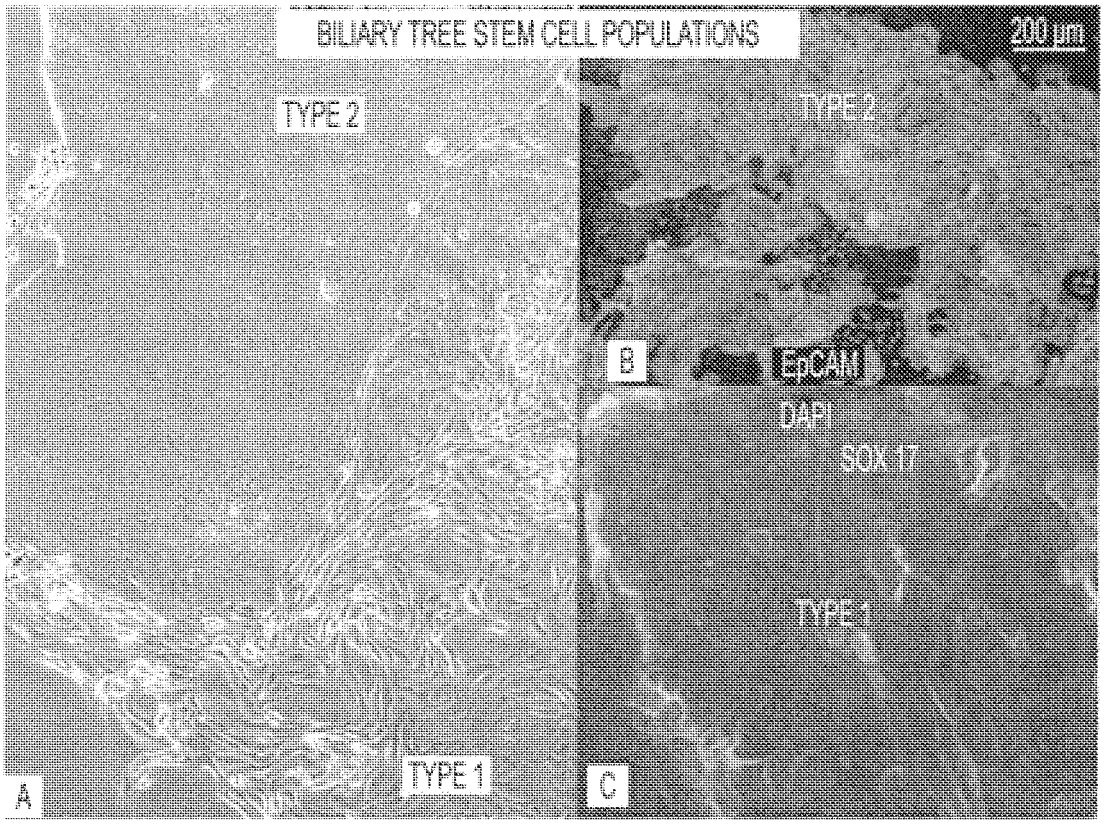

BILIARY TREE STEM CELL POPULATIONS
200 µm
TYPE 2
TYPE 1
A
B
EpCAM
DAPI
SOX17
TYPE 2
TYPE 1
C

FIG. 8

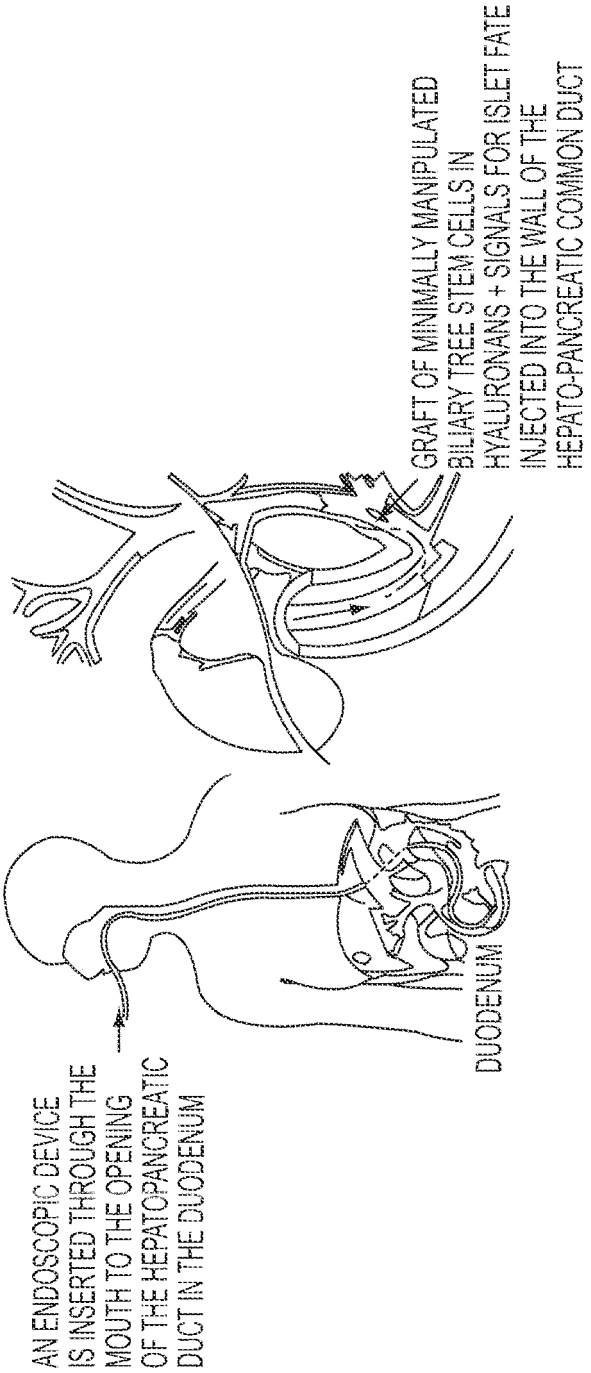

AN ENDOSCOPIC DEVICE IS INSERTED THROUGH THE MOUTH TO THE OPENING OF THE HEPATOPANCREATIC DUCT IN THE DUODENUM
DUODENUM
GRAFT OF MINIMALLY MANIPULATED BILIARY TREE STEM CELLS IN HYALURONANS + SIGNALS FOR ISLET FATE INJECTED INTO THE WALL OF THE HEPATO-PANCREATIC COMMON DUCT

FIG. 9

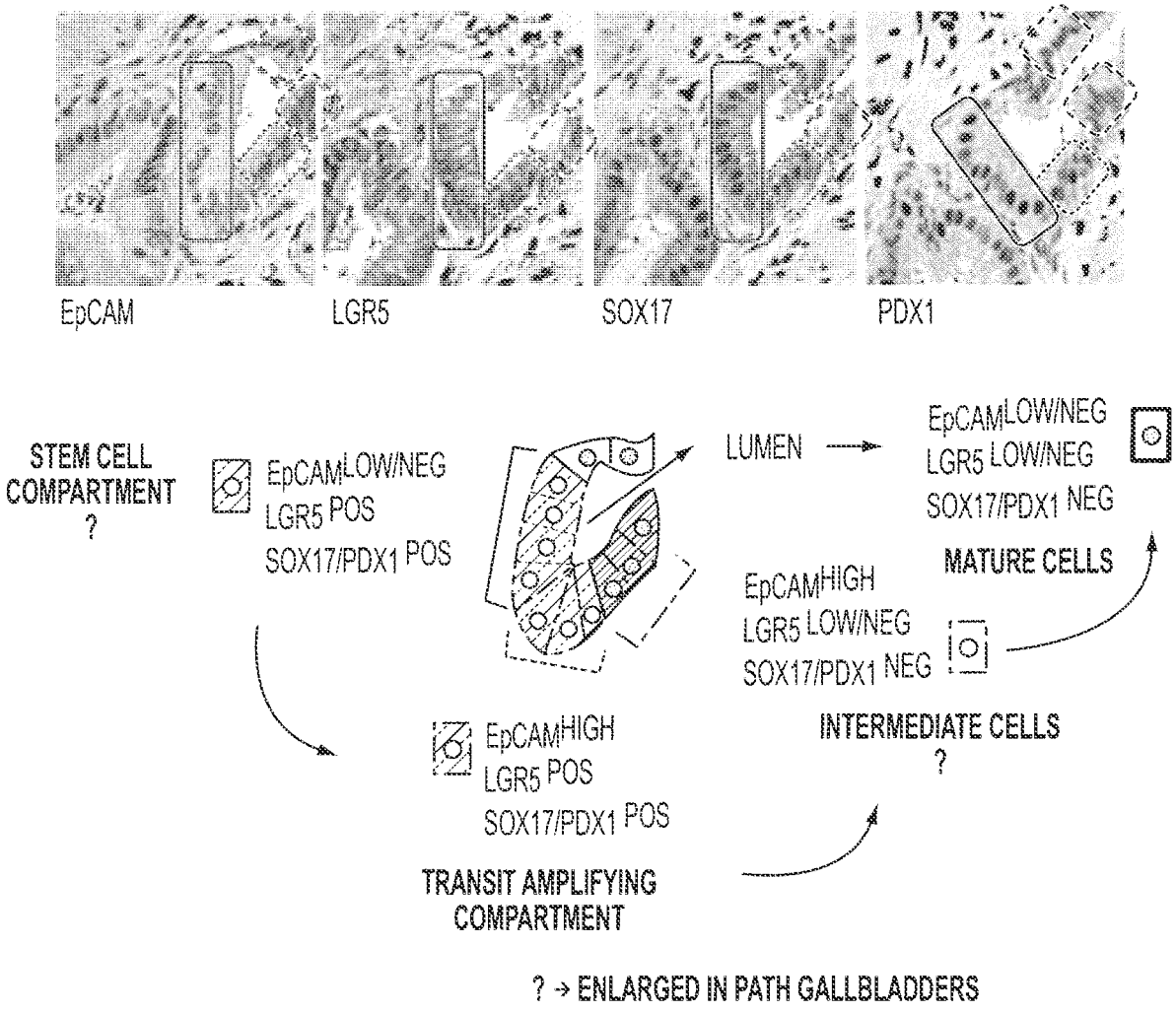

EpCAM
LGR5
SOX17
PDX1
STEM CELL COMPARTMENT ?
EpCAMLOW/NEG LGR5 POS SOX17/PDX1 POS
LUMEN
EpCAMLOW/NEG LGR5 LOW/NEG SOX17/PDX1 NEG
MATURE CELLS
EpCAMHIGH LGR5 LOW/NEG SOX17/PDX1 NEG
INTERMEDIATE CELLS ?
EpCAMHIGH LGR5 POS SOX17/PDX1 POS
TRANSIT AMPLIFYING COMPARTMENT
? → ENLARGED IN PATH GALLBLADDERS

FIG. 10